REMARKS/ARGUMENTS

STATUS OF THE CLAIMS

Claims 1-19 and 21-61 and 201-221 are pending with entry of this amendment, claims 201-221 being withdrawn, claims 20, 62-200 and 222-303 being cancelled. Claims 19, 21, 22, 29, 30, 36, 38, and 59 are amended herein. These amendments introduce no new matter and support is replete throughout the specification. These amendments are made without prejudice to renewal of the claims in their original form and are not to be construed as abandonment or dedication of the previously claimed subject matter or agreement with any objection or rejection of record.

With respect to claims 19, 21, 29, 36, and 59, support for the amendments can be found in the claims as originally filed and throughout the specification. With respect to claim 19, see, for example, the specification at paragraphs 211 and 414; see also Figure 6. With respect to claim 21, see, for example, the specification at paragraphs 212-214 and 415-416; see also Figures 7 and 8. With respect to claim 29, see, for example, the specification at paragraphs 215, 217, and 417-418; see also Figures 9-10. With respect to claim 36, see, for example, the specification at paragraphs 219 and 419; see also Figure 11. With respect to claim 59, see, for example, the specification at paragraph 421; see also Figure 13.

Applicants submit that no new matter has been added to the application by way of the above claim amendments. Accordingly, entry of the Amendment is respectfully requested.

The Action noted that claims 12 and 14-17 are withdrawn as being drawn to non-elected species. However, pursuant to MPEP 803.02, claims to non-elected species are held to be withdrawn if on examination the elected species is found to be anticipated or rendered obvious by prior art; otherwise, the Examiner's search is to be extended. Applicants therefore do not consider claims 12 and 14-17 to be withdrawn.

Applicants further note that, as indicated in the response to the restriction requirement filed March 3, 2005, claims 14-17 read on the elected species.

The action of April 19, 2005 included: acknowledgement of elections (item 1), status of the claims (item 2), objection to the specification (item 3), rejections for alleged indefiniteness (item 4), rejections for alleged anticipation (items 5-6), and rejections for

alleged obviousness (items 7-11). Applicants traverse all rejections and objections, to the extent that they may be applied to the amended claims, for the reasons noted herein.

THE INFORMATION DISCLOSURE STATEMENTS

Applicants note with appreciation the Examiner's thorough consideration of the references cited in the Information Disclosure Statements submitted on September 16, 2004 and September 24, 2004.

It was indicated that references 20 and 21 in the September 16, 2004 IDS were not considered. A utility application based on these two provisional applications has since been filed and published, and the published application is included on the attached 1449. Applicants request that the Examiner indicate consideration of the citation by initialing the 1449 document and providing a copy to Applicants.

OBJECTIONS TO THE SPECIFICATION (ACTION ITEM 3)

The specification was objected to for inclusion of an embedded hyperlink and/or other form of browser-executable code. Applicants note that the issue in this regard is whether the citation is browser executable or not (the Office has indicated that, as a policy matter, it does not wish published patents to include citations that are hyperlinked to other sites). To comply with the objection, Applicants have amended the internet citations to render them non browser executable. In light of the amendments to the specification, this objection should be withdrawn.

THE CLAIMS ARE FREE OF FAY (ACTION ITEM 5)

Claims 1-11, 18-20, 47, 48, 52, and 61 were rejected for alleged anticipation under 35 USC 102(b) by Fay et al. Applicants respectfully traverse these rejections.

In order for a reference to anticipate an invention, the reference must teach each and every element of the claimed invention.

Fay et al. describe photosensitive peptides. The peptides do not, however, include a first label. Thus, the photosensitive peptides of Fay et al. do not comprise an enzyme substrate and include a first label, wherein a first signal exhibited by the first label when the substrate is in its first state is distinguishable from a second signal exhibited by the first label when the substrate is in its second state as required by the claims. All elements of

the composition (e.g., the caged sensor) of claims 1 and 2 are, therefore, not taught by Fay et al. Similarly, with respect to claim 61, since the components of claims 1 and 2 are not disclosed by Fay et al., the components would not have been compiled to encompass the kit.

Although the Action argues that Fay et al. teach "a composition comprising a cell (col. 12, lines 1-5) comprising a caged sensor for detecting an activity of an enzyme," Applicants note that column 12 lines 1-5 of Fay et al. focus on activation of photosensitive compounds to *treat* different cells or tissues. Applicants note that lines 29 -36 of column 12 suggest that "any of a variety of conventional assays can be used for evaluating and testing the efficacy of a photosensitive caged peptide," emphasizing that the photosensitive peptides of Fay et al., unlike the enzyme sensors of the present invention, are not themselves designed for detection of enzyme activity since they do not include a substrate and a label sensitive to the state of that substrate.

Applicants note that while Fay et al. describe photosensitive peptides, substrates in particular are mentioned only in passing and certainly not in a context relevant to the claimed invention. Although the Action argues that Fay et al. at column 7 lines 7-21 teach a substrate that can be converted from a first to a second state by an enzyme, Applicants note that this section of Fay et al. describes caging of exemplary amino acid residues including lysine, phosphoserine, and phosphothreonine; it makes no reference to enzyme substrates.

Although the Action argues that Fay et al. at column 12 lines 57-67 teach a first label exhibiting a first signal when the substrate is in its first state and a second signal when the substrate is in its second state, Applicants note that the peptides described in column 12 are described as being inhibitors, not substrates, of calmodulin-dependent protein kinases; the inhibitors compete with the kinases for binding to calmodulin. In addition, in column 12, *calmodulin* is fluorescently labeled in order to determine activity of the inhibitor; the fluorescent label described by Fay et al. is thus not a label that is responsive to the state of the enzyme's substrate.

With respect to claims 3, 4, 7, and 9, although the Action argues that "Fay et al. teach the first caging groups preventing the enzyme from acting upon the substrate (col 1, lines 60-63) and inhibiting the enzyme from acting upon the substrate by at least about 90%

(activity is inhibited to less than 10%, col. 20, lines 20-27)," the photosensitive peptide described in lines 20-27 inhibits the activity of the enzyme MLCK by binding to calmodulin; it is not a substrate for MLCK that includes a label responsive to the state of the substrate. Furthermore, the percent inhibition quoted from lines 20-27 is the percent inhibition of the enzyme's (MLCK's) activity *in the presence of an inhibitor* of the enzyme's activity (inhibitor peptide 9-NPG-RS-20) - this number does not represent inhibition caused by caging groups on a substrate for the enzyme, and as such is irrelevant to the claims at issue. In addition, although inhibitor peptide 9-NPG-RS-20 is photosensitive, it is cleaved and *in*activated by exposure to light.

The action argues that "Fay et al. further teach first caging groups physically connected to the substrate and covalently attached to one or more molecules (col. 14, lines 47-53)." However, Applicants note that lines 47-53 refer to construction of hybrid cytotoxins, for example, by conjugating a toxin to a translocation domain and a receptor (column 14, lines 36-42), rather than to covalent attachment of caging groups to molecules. Even if, *arguendo*, Fay et al. describe, in other sections, caging groups covalently attached to peptides, the exemplary peptides are plainly not substrates for the enzymes being assayed that include a label responsive to the state of the substrate.

With respect to claims 5 and 6, as previously noted, Fay et al. do not teach a caged enzyme substrate or a first label meeting the limitations of the claims.

With respect to claim 8, the Action states that exposure to light of 350 nm "is encompassed by the recited range of between about 400 and 700 nm." Applicants note 350 nm lies outside the stated range.

With respect to claim 10, Applicants note that the sections of Fay et al. cited by the Action (column 4 lines 26-28 and column 6 lines 2-14) provide a definition of a peptide and a general description of techniques for synthesizing photosensitive caged peptides, respectively; they do not make reference to substrates.

With respect to claims 18-20, the Action argues "Fay et al. teach the enzyme being a protein kinase that phosphorylates tyrosine, serine and threonine (col. 13, lines 26-31, line 60)" and "further teach one polypeptide comprising the first label and substrate for the kinase (col. 13, lines 26-31)." Applicants note that column 13 lines 26-31 describe a method

for modulating (not detecting) protein kinase C activity, using an autoinhibitory peptide. The caged peptide described in this section is thus a caged inhibitor, not a substrate, for protein kinase C; the peptide does not include a serine or threonine residue that can be phosphorylated by protein kinase C, and thus it can not serve as a substrate for the kinase. In addition, the caged peptide lacks a label. Similarly, column 13 lines 60 and 50-64 refer to caging of a phosphorylated threonine residue in an inhibitor (not substrate) of protein phosphatase (not kinase); this inhibitor also lacks a label. Applicants note column 18 lines 6-15 describe synthesis of a caged tyrosine, but make no reference to incorporation of the caged tyrosine in a kinase substrate or any effects thereof (such as effects on binding of a kinase). Although the Action argues that col. 12, lines 57-67 of Fay et al. teach the first label located at the threonine residue and exhibiting a first signal when the residue is not phosphorylated and a second signal when the residue is phosphorylated, as noted above, lines 57-67 describe determination of the activity of an inhibitor (the molecule to be caged and uncaged in Fay et al.) of calmodulin-dependent protein kinase using fluorescently labeled calmodulin. The caged inhibitor does not comprise a substrate and a label, particularly not a label responsive to the state of the substrate, and thus does not correspond to a caged sensor of the present invention.

With respect to claims 47, 48, and 52, as described above, the photosensitive peptides of Fay et al. do not contain all the elements of the caged sensors of the present invention. Any association of the peptides of Fay et al. with cellular or subcellular delivery modules would thus still fail to meet the limitations of the claims at issue.

Additional points of distinction are present in the dependent claims, but because independent claims 1 and 2 are not anticipated, it is not necessary to address each additional point.

Because Fay et al. do not teach at least a caged sensor including a substrate and a first label that meets the limitations recited in the claims, the rejections must be withdrawn.

THE CLAIMS ARE FREE OF BARRETT (ACTION ITEM 6)

Claims 2 and 57-60 were rejected for alleged anticipation under 35 USC 102(b) by Barrett et al. Applicants respectfully traverse these rejections.

In order for a reference to anticipate an invention, the reference must teach each and every element of the claimed invention.

Barrett et al. describe methods and compositions for immobilizing anti-ligands at predetermined positions on the surface of a solid substrate. According to Barrett et al., caged binding members are attached to the surface. The caging groups are removed from the caged binding members at predetermined regions on the surface, and anti-ligands are bound to the now uncaged binding members at the predetermined regions. (See, e.g., column 2 lines 38-52.) The anti-ligands immobilized on the surface can then be used, for example, to detect ligand binding to the anti-ligands (see, e.g., column 2 lines 62-68). Barrett et al. do not describe a caged sensor for detecting an activity of an enzyme according to the present invention.

Even if, as the Action notes, Barrett et al. arguably lists substrates as potential anti-ligands and enzymes as potential ligands, Barrett et al. do not suggest use of substrate/enzyme pairs as anti-ligand/ligand pairs. Barrett et al. describe uses of immobilized anti-ligand arrays in the context of binding studies and screens for ligands having high affinity for the immobilized anti-ligands (e.g., at column 21, lines 31-33), not in the context of enzymatic activity assays in which the association between an enzyme and substrate is generally only transient. In addition, binding is the only interaction Barrett et al. describe between the ligand and the anti-ligand; modification of the anti-ligand by the ligand (in particular, modification of a substrate by an enzyme) is not taught.

The Action argues that Barrett et al. teach "a first label, wherein a first signal is exhibited by the first label when the substrate is in its first state (first state is unbound with no signal and second state is bound with a signal, col. 21, lines 36-44)." However, Applicants note that lines 36-44 describe binding of a labeled ligand to those anti-ligands on the surface having high affinity for the ligand. The Action considers the first state to be where the ligand (which the Action equates with an enzyme) is not bound to the anti-ligand (which the Action equates with a substrate) and the second state to be where the ligand is bound to the anti-ligand. This simply does not correspond with caged sensors as described in claim 2. In lines 36-44 from Barrett et al., the label is present on the surface if the ligand is

bound to the particular anti-ligand and not present on the surface if the ligand is not bound - there is no dependence whatsoever of the signal from the label *on the state of the anti-ligand.*

Furthermore, Barrett et al. do not teach one or more caging groups associated with the one or more molecules and inhibiting the enzyme from acting upon the substrate. Although the Action argues that Barrett et al. teach such caging groups, Applicants note that in Barrett et al. it is the *binding members* that are caged, not the anti-ligands (which the Action equates with the substrate). In addition, the caging groups prevent binding of the anti-ligands to the binding members; Barrett et al. do not teach the caging groups as inhibiting an enzyme from acting on a substrate.

Additional points of distinction are present in the dependent claims, but because independent claim 2 is not anticipated, it is not necessary to address each additional point.

Because Barrett et al. do not teach at least a caged sensor including a substrate and a first label and one or more caging groups that meets the limitations recited in the claims, the rejections must be withdrawn.

THE CLAIMS ARE NOT OBVIOUS (ACTION ITEMS 7-11)

Item 7

Claim 13 was rejected for alleged obviousness under 35 USC 103(a) over Fay et al. in view of Tsien et al. Applicants respectfully traverse these rejections.

Three requirements must be met for a *prima facie* case of obviousness. First, the prior art reference(s) must teach all of the limitations of the claims (M.P.E.P § 2143.03). Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention (M.P.E.P. § 2143.01). Third, a reasonable expectation of success is required (M.P.E.P. § 2143.02). The teaching or suggestion to combine and the expectation of success must be both found in the prior art and not based on Applicants' disclosure (M.P.E.P. §2143).

The Action argues that "Fay et al., as applied to claim 1, teach a composition comprising a cell comprising a caged sensor for detecting the activity of an enzyme, but fail to teach the enzyme being a protease." However, as described at length above, Fay et al. fail to teach a cell comprising a caged sensor for detecting activity of an enzyme. Adding the

identity of the enzyme as a protease from Tsien et al. to the teachings of Fay et al. thus does not result in the claimed invention. The suggested combination does not include all the limitations of the claim at issue, since it does not include at least a caged enzyme substrate and a first label responsive to the state of that substrate.

Motivation to combine the teachings of Fay et al. and Tsien et al. by including in the composition of Fay et al. monitoring the activity of a protease as taught in Tsien et al. is also lacking. The Action states that Tsien et al. "teach protease activity monitored through FRET (pg. 4, lines 2-23)." Applicants note that the tandem fluorescent protein construct described on page 4 is expressed in a cell. There is thus no motivation to combine this protein construct of Tsien et al., which is expressed *in vivo* from a recombinant nucleic acid construct, with the photosensitive peptides of Fay et al., which are chemically synthesized *in vitro*.

In addition, a *prima facie* case of obviousness cannot be established where the proposed combination of references changes the principal of operation of the prior art invention being modified (M.P.E.P. § 2143.01). As noted above, the protein construct described on page 4 of Tsien et al. is produced by expression in a cell. Combining this construct with the teachings of Fay et al. would require the protein construct to be chemically synthesized, and this would require modification of the principal of operation of this construct as described.

No specific suggestion or motivation is found in either Tsien et al. or Fay et al. to combine the teachings of the two references to produce a caged sensor like those of the present invention. The Examiner's argument that the references be combined therefore involves an improper hindsight reconstruction of the invention.

Moreover, a reasonable expectation of success has not been demonstrated. For example, as noted above, the protein construct described on page 4 of Tsien et al. is produced by expression in a cell, while the photosensitive peptides of Fay et al. are produced by in vitro chemical synthesis.

Because the suggested combination does not include all the limitations of the claim at issue, because motivation for combining the teachings of Tsien et al. and Fay et al. is

lacking, and because there is no reasonable expectation of success, the rejection should be withdrawn.

Item 8

Claims 21, 22, 24-27, 29, 30, 32-34, 36-39, 41-43, 45, and 46 were rejected for alleged obviousness under 35 USC 103(a) over Fay et al. in view of Craig et al. Applicants respectfully traverse these rejections.

Again, three requirements must be met for a *prima facie* case of obviousness: the prior art reference(s) must teach all of the limitations of the claims, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention, and a reasonable expectation of success is required.

These requirements are not met by the combination of Fay et al. and Craig et al., because the references do not teach all of the limitations of the claims.

With respect to claims 1 and 2 (and all their dependent claims), as described at some length above, Fay et al. do not teach a caged sensor including a substrate and a first label that meets the limitations recited in the claims.

With respect to claim 21 and dependent claims 22 and 24-27, the combination of Fay et al. and Craig et al. does not teach all the limitations of the claims. Although the Action argues that "Craig et al. teach a polypeptide comprising a substrate for a kinase (par. 0118-0122) comprising a first label and a quencher," Applicants note that Craig et al. actually describe measurement of kinase activity using *three* distinct peptides: 1) the substrate, 2) a first peptide partner that binds the substrate regardless of its modification state, and 3) a second peptide partner that binds the substrate only when it is modified. The first and second peptide partners are labeled with fluorophores capable of exhibiting FRET. This clearly does not teach the limitations of claim 21, in which *one* polypeptide comprises the substrate, the first label, and a second label or quencher. Furthermore, in paragraphs 0118-0122 of Craig et al., the two fluorophores labeling the first and second peptide partners interact when both partners are bound to the modified substrate, whereas claim 21 specifies that the first and second labels interact when the substrate is *not* phosphorylated and that phosphorylation of the substrate *prevents* the interaction of the labels.

Regarding claims 22 and 30, as noted above, column 18 lines 6-15 of Fay et al. describe synthesis of a caged tyrosine but make no reference to incorporation of the caged tyrosine in a kinase substrate or any effects thereof (such as effects on binding of a kinase). Fay et al. thus do not, as the Action alleges, teach first caging groups located on residues involved in binding the kinase. With respect to claims 24-25, while Craig et al. arguably teach phosphorylation of a substrate resulting in a conformational change in the substrate, Craig et al. do not teach this conformational change as preventing the interaction of the first label and the second label or quencher (which, as noted above, are not located on a single polypeptide in Craig et al., as they are in the claims at issue). With respect to claims 26-27 (and 33-34 and 42-43), Fay et al. do not describe a phosphobinder or second caging groups associated therewith. No phosphobinders are taught in Fay et al., and the methyl ester mentioned in column 7 lines 11-13 and referred to in the Action as allegedly equating to a second caging group is used to protect an α-carboxylic group during amino acid and peptide synthesis and thus does not correspond to a second caging group.

With respect to claim 29 and dependent claims 30 and 32-34, as noted previously, Fay et al. do not teach a first label. In addition, Fay et al. fail to teach a phosphobinder; column 7 describes caging a phosphoserine, phosphothreonine, or phosphopeptide, but it does not, as the Action alleges, describe a phosphobinder that binds to a phosphorylated substrate, either intra- or inter-molecularly. Furthermore, as described above, in Craig et al., the substrate and the two labels are located on separate peptides; one polypeptide does not include the substrate and the first label as in claim 29. The combination of Fay et al. and Craig et al. thus does not teach all the limitations of the claims.

Regarding claim 36 and dependent claims 37-39 and 41-43, in addition to failing to teach the first label and phosphobinder, Fay et al. fail to teach a second substrate and third caging groups meeting the limitations of the claims. As noted previously, column 18 lines 39-43 of Fay et al. do not describe a substrate including a caged tyrosine. Furthermore, column 18 lines 39-43, alleged in the Action to describe a second substrate associated with a third caging group, in fact describe an *inhibitor* - not a second substrate included in a single polypeptide with the first substrate - that is cleaved and *in*activated upon exposure to light (see, e.g., column 20 lines 25-27).

In addition, the combination of Fay et al. and Craig et al. fails to teach all the limitations of claim 36. Although the Action argues that Craig et al. teach a polypeptide substrate comprising a quencher and a third label, as described above, the labels of Craig et al. are on separate polypeptides from each other and from the substrate.

With respect to claims 37-39, Fay et al. fail to teach a second substrate. Column 19 line 60-column 20 line 5 describe two distinct photosensitive inhibitors, not two substrates as the Action alleges (and certainly not two substrates on a single polypeptide as is specified in the claims). Fay et al. also fail to teach first caging groups preventing phosphorylation of the first substrate and third caging groups preventing phosphorylation of the second substrate, in a single polypeptide. With respect to claim 41, Craig et al. fail to teach third and fourth labels.

With respect to claims 45 and 46, Craig et al. fail to teach a fifth label exhibiting a signal independent of the state of the substrate. Applicants note that the second label referred to in paragraph 0026 of Craig et al. appears to be the label on the second binding partner, which the Action previously equated with the first or second label or quencher.

Claims 23, 31, and 40 were rejected for alleged obviousness under 35 USC 103(a) over Fay et al. in view of Craig et al. further in view of Truong et al. Applicants respectfully traverse these rejections.

The suggested combination of Fay et al., Craig et al., and Truong et al. does not teach all the limitations of the claims. The Action alleges that Fay et al. in view of Craig et al. as applied to claims 21, 29, and 36 teach a polypeptide comprising a first and second label. However, as noted above, the combination of Fay et al. and Craig et al. fails to teach a single polypeptide comprising a substrate, caging groups, first label, second label, phosphobinder, second substrate, third label and/or fourth label, for example, meeting the limitations recited in the claims.

Since the combination of Fay et al. and Craig et al. fail to teach first and second labels, adding positional details regarding the labels from Truong et al. still fails to meet the limitations of the claims.

No specific suggestion or motivation is found in either Fay et al. or Craig et al. to combine the teachings of the two references to produce a caged sensor like those of the present invention. Similarly, no specific suggestion or motivation is found in Fay et al., Craig et al., or Truong et al. to combine the teachings of the references to produce a caged sensor like those of the present invention. The Examiner's argument that the references be combined therefore involves an improper hindsight reconstruction of the invention.

As described above, the suggested combination of Fay et al. and Craig et al., or of Fay et al., Craig et al., and Truong et al., does not teach all the limitations of the claims. Specifically, the suggested combinations fail to teach at least the following: a caged enzyme substrate and a first label responsive to the state of the substrate; one polypeptide comprising the substrate, the first label, and a second label or quencher; the first and second labels interacting when the substrate is not phosphorylated and not interacting when the substrate is phosphorylated; a conformational change preventing interaction of the first and second labels; a phosphobinder; second caging groups preventing the phosphobinder from binding the phosphorylated substrate; a second substrate; third caging groups; and third and fourth labels.

Furthermore, motivation to combine the teachings of Fay et al. and Craig et al., or of Fay et al., Craig et al., and Truong et al., is lacking. No suggestion to combine the teachings is present in the references. In addition, a reasonable expectation of success has not been demonstrated, since the suggested combination of the teachings of Fay et al. and Craig et al. (or of Fay et al., Craig et al., and Truong et al.) does not result in the present invention. The rejections should be withdrawn.

Item 9

Claims 28, 35, and 44 were rejected for alleged obviousness under 35 USC 103(a) over Fay et al. in view of Craig et al. further in view of Endo et al. Applicants respectfully traverse these rejections.

Again, three requirements must be met for a *prima facie* case of obviousness: the prior art reference(s) must teach all of the limitations of the claims, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention, and a reasonable expectation of success is required.

The combination of Fay et al., Craig et al., and Endo et al. fails to teach all of the limitations of the claims. Although the Action argues that "Fay et al. in view of Craig et al., as applied to claims 21, 29 and 36, teach a polypeptide comprising a phosphobinder," as described above, the combination of Fay and Craig fails to teach a single polypeptide comprising a substrate, caging groups, first label, second label, phosphobinder, second substrate, third label and/or fourth label, for example, meeting the limitations recited in the claims. Adding the SH2 domain described in Endo et al. as an exemplary phosphobinder still fails to meet the limitations recited in the claims. Specifically, the combination fails to teach at least the aforementioned single polypeptide comprising a substrate, caging groups, first label responsive to the state of the substrate, second label, phosphobinder, second substrate, third label and/or fourth label of the present invention.

Furthermore, motivation to combine the teachings of Fay et al., Craig et al., and Endo et al. is lacking. Endo et al. teach a JAB SH2 domain capable binding a tyrosine-phosphorylated JH1 domain in the context of inhibiting tyrosine kinase activity. There is no suggestion in Fay et al., Craig et al., or Endo et al. that such an SH2 domain be incorporated into a sensor for detection of enzyme activity such as those described in the claims.

The combination of Fay et al., Craig et al., and Endo et al. thus does not teach all the limitations of the claims. Furthermore, motivation to combine the teachings of the references is lacking. In addition, there is no reasonable expectation of success, since the suggested combination does not result in the present invention. Accordingly, the rejections must be withdrawn.

Item 10

Claims 51, 52, 53 and 56 were rejected for alleged obviousness under 35 USC 103(a) over Fay et al. in view of Marriott et al. Applicants respectfully traverse these rejections.

The combination of Fay et al. and Marriott et al. does not meet the requirements for a *prima facie* case of obviousness. For example, the combination does not teach all the limitations of the claims. Although the Action argues that "Fay et al., as applied to claims 1, 2 and 47, teach a composition comprising a polypeptide, which can be used to mediate introduction of a sensor into a cell," as described above at some length, Fay et al. do

not teach a caged sensor including a substrate and a first label that meets the limitations recited in the claims.

With respect to claim 51, the Action alleges that "Marriott et al. teach a caged polypeptide comprising a caging group to inhibit the mediation of the molecule into a cell (Fig. 1(b); pg. 331, last sentence left column-last sentence middle column)." Applicants note that the caged peptides described in this section were *microinjected* into cells; they did not comprise a cellular delivery module, and certainly not a caged cellular delivery module meeting the limitations recited in claim 51.

With respect to claims 53 and 56, Applicants note that Figure 1(a) and the section entitled "Caged peptides" on page 331 of Marriott et al. describe, in general terms, caged reagents including peptide inhibitors and activators. They do not describe a subcellular delivery module associated with a sensor and meeting the limitations recited in claim 53, nor do they described a caged subcellular delivery module meeting the limitations recited in claim 56. Applicants further note that Figure 1(b) and pages 332-333 of Marriott et al. do not describe caging a subcellular delivery module to prevent it from mediating subcellular delivery of an associated sensor.

The combination of Fay et al. and Marriott et al. thus does not teach all the limitations of the claims. For example, at least the limitations of a caged sensor comprising a substrate and a first label responsive to the state of the substrate, a caged cellular delivery module, and a caged subcellular delivery module are simply missing entirely from the combination of references. Furthermore, motivation to combine the teachings of the references is lacking. No suggestion to combine the teachings is found in the references. In addition, there is no reasonable expectation of success, since the suggested combination does not result in the present invention. The rejections should be withdrawn.

Item 11

Claims 49, 50, 54, and 55 were rejected for alleged obviousness under 35 USC 103(a) over Fay et al. in view of Marriott et al. further in view of McGall et al. Applicants respectfully traverse these rejections.

The combination of Fay et al., Marriott et al., and McGall et al. does not meet the requirements for a *prima facie* case of obviousness. For example, the combination does not teach all the limitations of the claims.

As described above, the combination of Fay et al. and Marriott et al. fails to teach all the limitations of claims 47 and 52, from which the claims at issue depend. McGall is alleged to teach a cellular or subcellular delivery module covalently attached to a molecule, which attachment is reversed by exposure to light. However, applicants note that McGall et al. actually describe immobilization of anti-ligands at defined sites on a surface. According to McGall et al., the surface is coated with caged thiol groups. The caging groups are removed at defined sites on the surface, and anti-begins are bound to the thiol groups now exposed at those sites. Ligands can then be (non-covalently) bound to the anti-ligands. No photolabile attachment is formed between the anti-ligands and ligands described in column 4 lines 26-66 of McGall et al..

The combination of Fay et al., Marriott et al., and McGall et al. thus does not teach all the limitations of the claims. Specifically, at least the following limitations are simply not taught by the combination: a substrate and a first label responsive to the state of the substrate, with associated caging groups, photolabile attachment of a cellular delivery module to the one or more molecules including the substrate, and photolabile attachment of a subcellular delivery module to the one or more molecules including the substrate. Furthermore, motivation to combine the teachings of the references is lacking. In addition, there is no reasonable expectation of success, since the suggested combination does not result in the present invention. The rejections should be withdrawn.

THE CLAIMS, AS AMENDED, ARE DEFINITE (ACTION ITEM 4)

35 USC §112, Paragraph 2 Rejection of Claims 1-11, 13, and 18-61

Claims 1-11, 13, and 18-61 were rejected for alleged indefiniteness because it was allegedly unclear how the first caging groups are associated with the one or more molecules, whether the first caging groups are considered part of the first state of the substrate, and whether the enzyme can act on the substrate while the first caging groups are associated with the one or more molecules. Applicants respectfully traverse these rejections.

The claims were rejected because it was allegedly unclear how the first caging groups are associated with the one or more molecules. Applicants note that *how* the caging groups are associated with the one or more molecules is not relevant to the claims at issue; claims 1 and 2, for example, simply require that the caging groups *be* associated (and that they inhibit the enzyme from acting upon the substrate). Therefore, the language of the claims creates no issue with respect to lack of clarity. However, Applicants also note that the specification provides extensive guidance as to how various caging groups can be associated with various molecules. See, e.g., paragraphs 150-152, 203, and 353-360, which indicate that caging groups can be covalently or noncovalently associated with molecules, that a single caging group can be covalently attached to an amino acid side chain required for activity, that caging groups can be attached to a motif recognized by an enzyme, that caging groups can physically trap an active molecule in a framework formed by the caging groups, and that a caging group can be covalently attached to a molecule by a photolabile linker, among many other examples. Guidance for determining useful sites of attachment of caging groups to molecules is provided, e.g., in paragraph 360. A large number of exemplary caging groups for which methods of attachment to various molecules have been described are provided, e.g., in paragraphs 353-355 and 357-359. There is nothing indefinite about the phraseology at issue: how the caging groups are associated is irrelevant, since the claims simply specify that they are associated. Accordingly, the rejection should be withdrawn.

The claims were also rejected because it was allegedly unclear whether the first caging groups are considered part of the first state of the substrate. A complete reading of claims 1 and 2 and of the specification, e.g., at paragraphs 198, 199, and 204, makes it clear that the caged sensor includes a) one or more molecules comprising the substrate, wherein the substrate is in a first state, and b) one or more first caging groups associated with the one or more molecules. The caging groups are thus clearly not considered to be part of the first state of the substrate. Accordingly, there is nothing indefinite about the phraseology at issue, and the rejection should be withdrawn.

The claims were also rejected because it was allegedly unclear whether the enzyme can act on the substrate while the first caging groups are associated with the one or more molecules. A complete reading of claims 1-4 makes it clear that the caging groups can

either partly inhibit or entirely prevent the enzyme from acting on the substrate while the caging groups are associated with the one or more molecules. Claims 1 and 2 specify that the caging groups inhibit the enzyme from acting on the substrate. Claim 3 provides several exemplary percentages by which the caging groups can inhibit the enzyme from acting on the substrate, and claim 4 indicates that in certain embodiments the caging groups prevent the enzyme from acting upon the substrate. Accordingly, there is nothing indefinite about the phraseology at issue, and the rejection should be withdrawn.

Claim 4 was rejected because it was allegedly unclear whether the first caging groups require any further product limitations in order to prevent the enzyme from acting on the substrate. Applicants respectfully traverse this rejection. Applicants note that independent claims 1 and 2, from which claim 4 depends, cover embodiments in which the caging groups inhibit the enzyme from acting on the substrate - which includes a subset of embodiments in which the caging groups prevent the enzyme from acting on the substrate. Claim 4 simply specifies products that fall into this subset. There is nothing indefinite about claiming those species in which the caging groups prevent action of the enzyme on the substrate. Accordingly, the rejection should be withdrawn.

Claim 5 was rejected as being allegedly unclear as to whether removal of the caging groups requires any further product limitations, and the Action alleges that the claim is drawn to a method of removing caging groups. Applicants respectfully traverse this rejection. Claim 5 specifies that the caging groups possess certain physical properties: removal of the caging groups can permit the enzyme to act upon the substrate, or an induced conformational change in the caging groups can permit the enzyme to act upon the substrate. The use of physical property limitations in claiming compositions has long been accepted by the Office. One can plainly tell whether any composition meets the relevant physical property limitation of the claim - which is all that the law requires in this context. Therefore, there is nothing indefinite about the phraseology at issue, and the rejection should be withdrawn.

Claim 11 was rejected because it was allegedly unclear whether the composition comprises the same enzyme, cell, or cell sensor as those recited in claim 2, and allegedly vague as to whether the composition comprises more than one enzyme, cell, or cell

sensor. Applicants respectfully traverse this rejection. A complete reading of claims 2 and 11, with attention to antecedent basis, makes it clear that claim 2 describes a caged sensor for detecting an activity of an enzyme. The enzyme itself is not required to be present in the composition of claim 2, and no cell or cell lysate is recited in this claim. Claim 11 indicates that the composition of claim 2 can include *the* enzyme (i.e., the enzyme corresponding to the caged sensor of claim 2), *a* cell, *a* cell comprising *the* caged sensor (i.e., the caged sensor of claim 2), *a* cell comprising *the* enzyme (i.e., the enzyme corresponding to the caged sensor of claim 2), or *a* cell lysate. Accordingly, there is nothing indefinite about the phraseology at issue. The rejection should be withdrawn.

Claims 19, 29, and 36 were rejected because they were allegedly unclear whether the one polypeptide is the same as the one or more molecules recited in claim 1 or 2 or whether the composition further comprises another molecule being a polypeptide, and whether the one or more molecules comprise the polypeptide or if the polypeptide is the substrate. A complete reading of each of these claims and claim 1 or 2, with attention to antecedent basis, makes it clear that since one polypeptide comprises the first label and the substrate for the kinase, the one polypeptide must be one of the one or more molecules collectively comprising a substrate and a first label in claim 1 or 2. However, in the interest of expediting prosecution, Applicants have amended the claims to render the rejection moot. The amended claims explicitly recite that the one or more molecules include the one polypeptide. Accordingly, the rejection should be withdrawn.

Claims 23, 31, and 40 were rejected as being allegedly unclear whether the serine, threonine, or tyrosine residue must also be located at the N- or C-terminus since the first label is located at the serine, threonine or tyrosine residue. Applicants respectfully traverse this rejection. Claim 19 specifies that the first label is located at the serine, threonine or tyrosine residue. However, claims 23, 31, and 40 do not depend from claim 19 and do not include this limitation. The first label is thus not necessarily located at the serine, threonine or tyrosine residue in these claims. The rejection is therefore moot and must be withdrawn.

Claims 22 and 30 were rejected as being allegedly unclear how amino acid residues are involved in binding the kinase, and if the kinase binds directly to these amino acids or if the amino acids merely assist in the binding of kinase. Applicants maintain that

the phraseology at issue is clear to one of skill in the art. However, in the interest of expediting prosecution, Applicants have amended the claims to render the rejection moot. Accordingly, the rejection must be withdrawn.

Claim 25 was rejected because it was allegedly unclear whether triggering a conformational change in the polypeptide requires any product limitations, and the Action alleges that the claim is drawn to a method of triggering a conformational change. Applicants respectfully traverse this rejection. Claim 25 specifies that the caged sensor possess certain physical properties: that phosphorylation of the substrate triggers a conformational change in the polypeptide, which conformational change prevents the interaction of the first label and the second label or the quencher, or that phosphorylation of the substrate results in binding of a phosphobinder to the phosphorylated substrate, which binding prevents the interaction of the first label and the second label or the quencher. The use of physical property limitations in claiming compositions has long been accepted by the Office. Conformation is, plainly, a structural and physical property of the molecule, and is therefore a completely appropriate basis for a claim limitation. One can plainly tell whether any composition meets the relevant physical property limitation of the claim - which is all that the law requires in this context. Therefore, there is nothing indefinite about the phraseology at issue, and the rejection should be withdrawn.

The claim was further rejected because it was allegedly vague as to whether a phosphobinder is required to bind to the substrate or whether the conformational change occurs by other means. A complete reading of the claim and the supporting passages of the specification (e.g., paragraphs 212-214 and 415-416, as well as Figures 7 and 8) make it clear that a phosphobinder is not necessarily required. In one embodiment, as described in paragraph 213, phosphorylation of the substrate triggers a conformational change in the polypeptide, and this conformational change prevents interaction of the first label and the second label or the quencher. This embodiment does not require the presence of a phosphobinder. In one embodiment, as described in paragraph 214, phosphorylation of the substrate results in binding of a phosphobinder to the phosphorylated substrate, and this binding prevents the interaction of the first and the second label or the quencher. In this embodiment, the substrate may or may not undergo a conformational change; it is the

binding of the phosphobinder to the phosphorylated substrate that results in production of the second signal. Accordingly, there is nothing indefinite about the phraseology at issue. The rejection should be withdrawn.

Claims 25-44 were rejected because allegedly the term "phosphobinder" is vague and indefinite and not defined in the specification, and because allegedly it is unclear what compounds are encompassed by a phosphobinder and if a phosphobinder is any compound or molecule that is capable of binding to a phosphorylated substrate. Applicants note that in the first sentence of paragraph 416, a phosphobinder is indicated to be a specific binder that binds to the phosphorylated substrate. Applicants further note that a number of exemplary phosphobinders are described in the specification, e.g., at paragraphs 18, 214, 350, 405-406, and 416-417. Examples listed in the specification include: an antibody, an anti-phospho Tyr antibody, an anti-phospho Ser antibody, an anti-phospho Thr antibody, an SH-2 domain, a PTB domain, a 14-3-3 domain, an FHA domain, a WD40 domain, a WW domain, and a metal chelator, among others. Accordingly, there is nothing indefinite about the phraseology at issue, and the rejection should be withdrawn.

Claims 27, 34, 39, and 43 were rejected because they were allegedly unclear what product limitations are required for the first, second, and third caging groups to be removed under different conditions. Applicants note that caging groups and removal of caging groups to uncage caged components are discussed in detail throughout the specification, with respect to a variety of embodiments of the invention (e.g., at paragraphs 45, 56, 150, 174, 217-219, 284, 300, 302, 403, and 417). Reference to any of these sections, for example, makes it clear that caged components can be uncaged by exposure to appropriate conditions, e.g., light of suitable wavelength, sonication, pH, or heat, *inter alia*. A variety of exemplary caging groups, and conditions for their removal, are noted in the specification, e.g., at paragraphs 353-361; these examples include photolabile caging groups removable by different wavelengths of light as well as caging groups removable by application of an electric or magnetic field, a change in pH and/or ionic strength, temperature, addition of an antigen or saccharide, or other environmental variables. A complete reading of the claims and the relevant portions of the specification clearly indicate that caging groups removable under different conditions are, quite simply, caging groups that

can be removed by exposure to distinct conditions: two different wavelengths of light, light and heat, light and sonication energy, etc. The claims were further rejected because it was allegedly unclear if the caging groups must have different wavelengths for removal or if they must only be different caging groups. Applicants note that the different caging groups are optionally removable by different wavelengths of light, as noted in the Action, but are optionally removable by means other than uncaging light. As would be evident to one of skill in the art, caging groups removable under different conditions will typically be chemically different. However, Applicants note that if, as the Action suggests, the first, second, and third caging groups were to "only be different caging groups" that were removable by the same wavelength of light, they would obviously not meet the limitation of the claim at issue that the caging groups be removable under different conditions. Accordingly, there is nothing indefinite about the phraseology at issue, and the rejection should be withdrawn.

Claims 29 and 36 were rejected because they allegedly do not appear to recite any further product limitations to the composition of claim 18, and the Action alleges that the claims are drawn to methods such as phosphorylation of the substrate resulting in binding of a phosphobinder and the first and second label not interacting when the substrate is not phosphorylated. Applicants respectfully traverse this rejection. Claim 29 specifies that the caged sensor possess certain physical properties: that the first label and the second label or the quencher do not interact when the substrate is not phosphorylated and that phosphorylation of the substrate results in intramolecular binding of the phosphobinder to the phosphorylated substrate, which binding results in the interaction of the first label and the second label or the quencher, or that the first label and the second label or the quencher do not interact when the substrate is not phosphorylated and that phosphorylation of the substrate results in intermolecular binding of the phosphobinder to the phosphorylated substrate, which binding results in the interaction of the first label and the second label or the quencher. Similarly, claim 36 specifies that the caged sensor possess certain physical properties: that the third label and the fourth label or the quencher do not interact when the second substrate is not phosphorylated and that phosphorylation of the second substrate results in intramolecular binding of the phosphobinder to the phosphorylated second

substrate, which binding results in the interaction of the third label and the fourth label or the quencher. As noted above, the use of physical property limitations in claiming compositions is well accepted. Conformation is, plainly, a structural and physical property of the molecule, as is ability to associate with a specified molecule, and is therefore a completely appropriate basis for a claim limitation. One can plainly tell whether any composition meets the relevant physical property limitation of the claim - which is all that the law requires in this context. Therefore, there is nothing indefinite about the phraseology at issue, and the rejection should be withdrawn.

The claims were further rejected because it was allegedly unclear whether the physical limitation of a phosphobinder is intended to be part of the composition or if a polypeptide comprising a substrate for kinase and a first and second label would be able to bind a phosphobinder, and whether Applicant is claiming a phosphobinder attached to a phosphorylated substrate or if the peptide is meant to comprise only a substrate that has not been phosphorylated. The amendments to the claims render the rejections moot. However, to the extent the rejections are applied to the amended claims, Applicants traverse. As the amendments to the claims make clear, the one or more molecules include one polypeptide comprising the substrate and a phosphobinder (in the first alternative in claim 29 or in claim 36) or a first polypeptide comprising the substrate and a second polypeptide comprising a phosphobinder (in the second alternative in claim 29). The phosphobinder is thus clearly part of the composition. As indicated in the claims, the composition includes a substrate that is in a first state on which the enzyme can act (i.e., in these embodiments, a substrate that can be phosphorylated by the kinase), and that when phosphorylated is capable of binding to the phosphobinder. Applicants note that when the substrate and the phosphobinder are part of a single polypeptide, as in the first alternative in claim 29 or in claim 36, the substrate and phosphobinder are in some sense attached to each other whether or not the substrate has been phosphorylated and bound by the phosphobinder. Accordingly, there is nothing indefinite about the phraseology at issue, and the rejection should be withdrawn.

Claims 48 and 53 were rejected as allegedly unclear whether the composition further comprises a polypeptide or whether the cellular delivery module and subcellular delivery module are a polypeptide which is the one or more molecules recited in claims 1 and

2. A complete reading of claim 48 in the context of claim 47, from which it depends, indicates that the one or more molecules are associated with a cellular delivery module; the cellular delivery module is thus clearly not equivalent to the one or more molecules. Similarly, a complete reading of claim 53 in the context of claim 52, from which it depends, indicates that the one or more molecules are associated with a subcellular delivery module; the subcellular delivery module is thus clearly not equivalent to the one or more molecules. Accordingly, there is nothing indefinite about the phraseology at issue, and the rejection should be withdrawn.

Claim 59 was rejected because it was allegedly unclear whether the first and second oligonucleotides are the one or more molecules recited in claims 1 and 2, or whether the composition comprises the one or more molecules as well as the first and second oligonucleotides. The claim has been amended to indicate that the sensor further comprises the first oligonucleotide. As indicated, the second oligonucleotide is bound to a matrix. The rejection is therefore moot and should be withdrawn.

CONCLUSION

In view of the foregoing, Applicant(s) believe(s) all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, an interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 337-7871 to schedule an interview.

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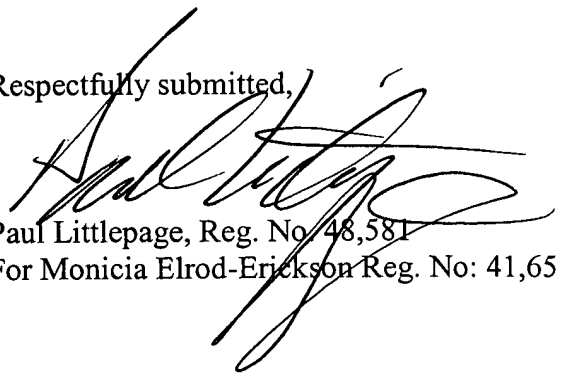
Respectfully submitted,



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Attachments:

1) A petition to extend the period of response for two months;
2) A transmittal sheet;
3) Information Disclosure Statement with 1449; and,
4) A receipt indication postcard.